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Clinical Pharmacology of Imipenem and Cilastatin in Premature Infants during the First Week of Life

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The first-dose and multidose pharmacokinetics of imipenem and cilastatin were evaluated in 41 premature infants during their first week of life. Premature infants (gestational age, ≤37 weeks) were assigned to receive 10-, 15-, 20-, or 25-mg/kg doses of imipenem-cilastatin (1:1) as a single- or multiple-dose regimen. A total of 39 infants received a single dose, whereas 18 infants received multiple doses. No differences were observed in pharmacokinetic parameter estimates for either agent relative to the dose administered or infant body weight; thus, the data were pooled. Elimination half-life, steady-state volume of distribution, and body clearance averaged 2.5 h, 0.5 liter/kg, and 2.5 ml/min per kg, respectively, for imipenem and 9.1 h, 0.4 liter/kg, and 0.5 ml/min per kg, respectively, for cilastatin. Similar values for these parameter estimates were observed after multidose administration, although substantial accumulation of cilastatin in serum was observed. A total of 21% of the imipenem and 43% of the cilastatin were excreted unchanged in the urine over a 12-h collection period. Corresponding renal clearances averaged 0.4 and 0.2 ml/min per kg for imipenem and cilastatin, respectively. Substantial differences were observed in the route by which imipenem was cleared from the body compared with data from adult volunteers. These data suggest that infants should receive an imipenem dose of 20 mg/kg administered every 12 h for the treatment of bacterial infections outside the central nervous system.

Despite recent advances in the care of seriously ill premature infants, bacterial infections continue to be an important cause of infant morbidity and mortality (10, 17–19). Common pathogens responsible for infections during the first month of life include *Streptococcus agalactiae* (group B streptococcus), the enterococci, enteric gram-negative bacilli, and *Listeria monocytogenes*. To provide for adequate antibacterial therapy against these pathogens, initial empiric regimens for these infants routinely require a combination of antibiotics. Although antibiotic combinations that include an aminoglycoside and a β-lactam or an expanded-spectrum cephalosporin and a penicillin have frequently been successful in the treatment of infections in these infants, drug-related toxicities and the development of resistant microorganisms underscore the importance for continual evaluation of more effective, less toxic compounds (1, 8, 13–15, 19).

Imipenem, the stable derivative of thienamycin, represents the first of a new class of β-lactam antibiotics (14). The drug possesses potent in vitro activity against a broad spectrum of aerobic and anaerobic gram-positive and gram-negative bacteria, including the majority of pathogens responsible for neonatal infections (4, 14). Clinically, the drug is coadministered with cilastatin, a compound which possesses no inherent antibacterial activity. Cilastatin inhibits the renal metabolism of imipenem by the brush border enzyme dehydropeptidase I.

In order to use the drug safely and effectively in premature infants, the clinical pharmacology of imipenem and cilastatin in these patients must be described prior to dose selection and the initiation of clinical efficacy trials. The purpose of the present study was to characterize the first-dose and multidose pharmacokinetics of imipenem and cilastatin in premature infants during the first week of life.

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MATERIALS AND METHODS

Infants (gestational age, ≤37 weeks; weight, ≥700 g) admitted to the newborn intensive care unit of Rainbow Babies and Childrens Hospital with a suspected or documented bacterial infection were eligible for enrollment in this study. Gestational age was estimated by the maternal menstrual history and by physical examination by the method of Dubowitz et al. (6). All infants received concurrent conventional antibiotic therapy during the study period. This study was approved by the Institutional Review Board for Human Subjects Investigation of the University Hospitals of Cleveland, and informed, written consent was obtained from the parent or guardian of each infant.

Prior to study drug administration, a maternal history was obtained; a complete physical examination of the infants was performed; and blood was obtained from the infants for the determination of serum electrolytes, creatinine, urea nitrogen, calcium, phosphorous, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alanine aminotransferase, total and direct bilirubin, total protein, albumin, and complete blood count with differential and platelet count. Urine was sent to a laboratory for urinalysis. These laboratory evaluations were performed prior to study drug administration and again, at a minimum, upon completion of the study. Laboratory deter-

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minations were performed by the clinical laboratories of the University Hospitals of Cleveland.

Drug administration and sample collection. Imipenem was supplied as a sterile crystalline powder equivalent to 500 mg and cilastatin was supplied as a sterile solution equivalent to 500 mg/10 ml (Merck Sharp & Dohme Research Laboratories, West Point, Pa.). Imipenem powder was reconstituted with 10 ml of cilastatin and further diluted in an appropriate admixture solution prior to administration. This intravenous admixture solution containing imipenem and cilastatin in a 1:1 ratio was administered intravenously over 15 to 30 min. For the first dose and again at the multidose evaluation, the drug was administered via an autosyringe by a research nurse.

By protocol design, the first three study infants weighed >1,200 g and received a single 15-mg/kg dose of imipenem-cilastatin. In the absence of any drug-associated toxicity, the next three infants enrolled in the study received multiple-dose imipenem-cilastatin at 15 mg/kg every 12 h for six or more doses. In a sequential escalating fashion, subsequent infants were enrolled in the study to receive 20- and 25-mg/kg doses if they weighed >1,200 g and 10-, 15-, 20-, and 25-mg/kg doses if they weighed <1,200 g. Single-dose determinations were completed in groups of three infants before initiating multidose evaluations at each dose level. Furthermore, data analysis of each dose level was completed before infants were enrolled in the study of the next higher dose level. This seemingly cumbersome and potentially confusing drug dosing protocol was undertaken in an attempt to minimize further potential risks to our study infants.

Venous blood samples (≤0.5 ml) for the determination of imipenem and cilastatin in serum were obtained at time zero; immediately upon completion of the infusion (i.e., 15 to 30 min); and at 60, 120, 240, and 480 min after the beginning of the infusion. Blood sampling protocols under multidose conditions identical to those described above for single-dose conditions were performed after infants received a minimum of 3 days of uninterrupted drug administration every 12 h.

Blood was collected in sterile glass tubes, allowed to clot, and immediately centrifuged. Serum was removed and stabilized with 1 volume of 1 M morpholineethanesulfonic acid buffer (pH 6.0), urine was stabilized with 1 volume of 0.5 M morpholinepropanesulfonic acid, (pH 6.8), and both samples were stored at −70°C until they were analyzed. This stabilization procedure for serum is necessary to inhibit imipenem hydrolysis under routine storage conditions (20). Before administration of the first drug dose, a urine sample was obtained; thereafter, urine was obtained as timed portions from 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after drug administration.

Drug assay. The concentrations of imipenem and cilastatin in both serum and urine were determined by high-pressure liquid chromatography as described previously (20). For cilastatin, late peaks were routinely removed from the column by a 3-min, 40% methanol wash following the elution of the cilastatin peak. Urine was injected directly after removing particulate matter by centrifugation and making a 5- to 20-fold dilution of the supernatant. The assay limit of detection was 0.3 mg/liter for imipenem and 0.5 mg/liter for cilastatin. The assay was linear up to 100 mg/liter, with 99% recovery. The within-day coefficients of variation ranged from 1.8 to 6.4% at 2- to 20-mg/liter concentrations, and the between-day coefficients of variation ranged from 3.2 to 3.9%.

Pharmacokinetic analysis. Imipenem and cilastatin concentrations in serum from each patient were plotted against time on a semilogarithmic scale. The pharmacokinetics of imipenem and cilastatin were characterized by standard noncompartmental techniques (11). The area under the serum concentration-time curve (AUC) was obtained by using the linear trapezoidal rule method up to the final measured concentration in serum and extrapolated to infinity after the first dose. The elimination half-life ($t_{1/2}$) was determined by using the postdistributive terminal portion of the serum concentration-time curve. Total body clearance (CL) was determined by using the formula dose/AUC from 0 h to infinity following the first dose. The apparent steady-state volume of distribution (V_{ss}) was determined by the equation $V_{ss} = (\text{dose} \cdot \text{AUMC})/\{\text{AUC}^2 - [(\text{dose} \cdot T)/(\text{AUC} \cdot 2)]\}$, where AUMC is the area under the first moment of the concentration-time curve and T is the infusion duration. Pharmacokinetic parameters determined under multidose conditions were determined as described above on drug concentration-time data converted to first dose by using the superposition method (3). The renal clearance (CL_R) of imipenem and cilastatin for each patient was calculated as $CL_R = A_{0-\tau}/AUC_{0-\tau}$, where A is the cumulative amount of drug excreted (23). Nonrenal clearance (CL_{NR}) was determined by subtracting CL_R from CL. Statistical evaluations were performed by using the paired and unpaired Student t test, analysis of variance, and regression analysis.

TABLE 1. Characteristics of study infants[a]

Characteristic	Mean ± SD	Range
Gestational age (wk)	29.0 ± 3.2	22–36.5
Postnatal age (days)	2.6 ± 1.1	1–6
Body wt (g)	1,187 ± 386	670–1,890
Surface area (m^2)	0.11 ± 0.02	0.08–0.15
Serum creatinine (mg/dl)	1.1 ± 0.2	0.4–1.4

[a] There were 20 male and 21 female infants.

RESULTS

Forty-one preterm infants were enrolled in our study. The characteristics of these study infants are given in Table 1. All 41 infants were studied after administration of a single dose, and 18 infants were reevaluated after multidose drug administration. Concentration in serum data sets obtained after the first dose in two patients were excluded from data analysis because of errors in sample collection. Thus, we report here on 39 infants after single-dose administration and on 18 infants after multidose administration of imipenem-cilastatin. Of the latter 18 infants, 16 represent matched pairs, i.e., combined first-dose and multidose evaluations. No biochemical, functional, or clinical toxicity was associated with the administration of imipenem-cilastatin in any infant.

Figures 1 and 2 depict the overall imipenem and cilastatin serum concentration-time curves obtained after first-dose and multidose administrations, respectively. Peak concentrations of both agents in serum were observed at the completion of the intravenous infusion and correlated directly with the dose administered (for imipenem, $r = 0.54$ and $P < 0.001$; for cilastatin $r = 0.64$ and $P < 0.001$). Imipenem concentrations in serum averaged 22.6, 34.8, 46.7, and 55.9 mg/liter 30 min after the beginning of intravenous drug administration and 2.3, 3.5, 4.3, and 4.5 mg/liter at 8 h after the first imipenem-cilastatin dose of 10, 15, 20, and 25 mg, respectively (Fig. 1). Much higher concentrations after the first dose (Fig. 1) and marked accumulation with repetitive dosing every 12 h (Fig. 2) were observed with cilastatin.

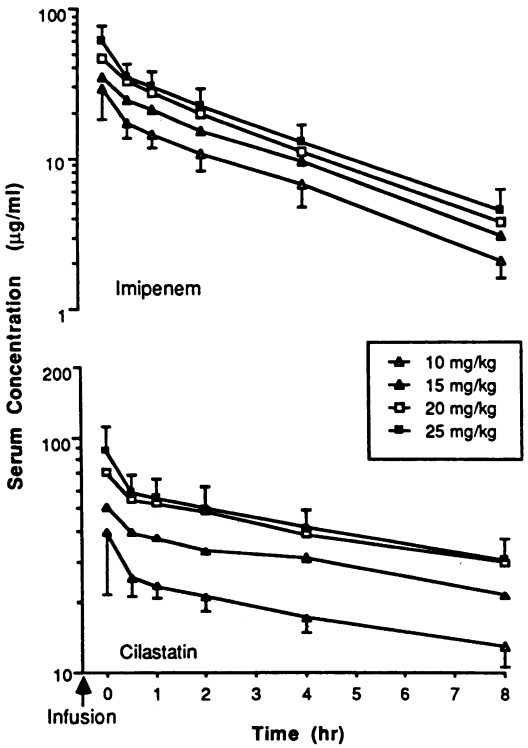

FIG. 1. Overall mean ± standard deviation serum concentration-time curve for imipenem and cilastatin after intravenous single-dose administration of different doses.

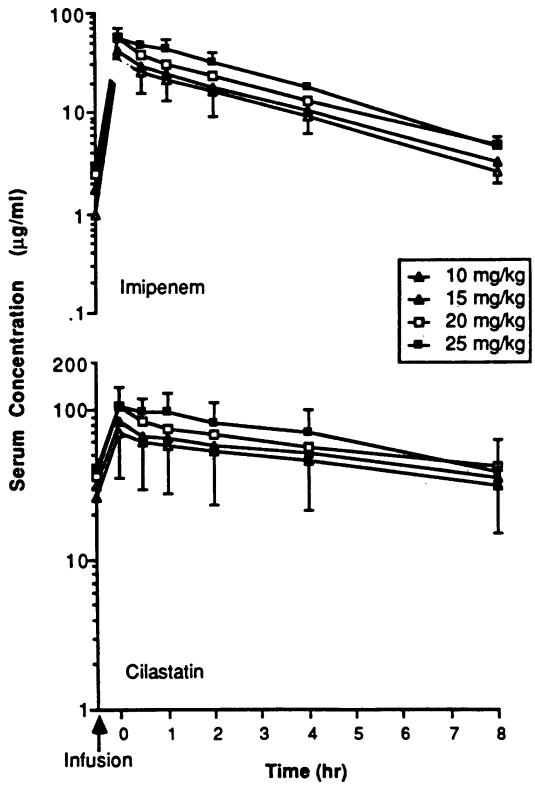

FIG. 2. Overall mean ± standard deviation serum concentration-time curve for imipenem and cilastatin after intravenous multidose administration of different doses.

In contrast, no accumulation of imipenem in serum was observed after multiple doses (Fig. 2). Cilastatin concentrations in serum exceeded those of imipenem throughout the 8-h sampling period (Fig. 1 and 2).

First-dose pharmacokinetic parameter estimates for imipenem and cilastatin relative to the four different doses administered are given in Tables 2 and 3, respectively. Analysis of variance revealed no differences in pharmacokinetic parameter estimates for either imipenem or cilastatin relative to the dose administered or infant body weight; thus, the data were pooled for further presentation and evaluation. Pharmacokinetic parameter estimates for imipenem were significantly different ($P < 0.001$) from those observed for cilastatin after the first dose (Tables 2 and 3) and for all but V_{ss} after multidose administration. As would be expected, the AUC for both compounds increased with increasing dose (Tables 2 and 3). Evaluation of the relationship between drug dose (in milligrams per kilogram) and AUC after the first dose revealed a positive linear relationship for both imipenem ($r = 0.64$, $P < 0.001$) and cilastatin ($r = 0.56$, $P < 0.001$). A similar relationship was observed under multidose conditions (for imipenem, $r = 0.86$ and $P < 0.001$; for cilastatin, $r = 0.79$ and $P < 0.001$).

Comparisons of first-dose and multidose pharmacokinetic parameter estimates for imipenem and cilastatin are given in Table 4. No differences were observed between first-dose and multidose evaluations for either imipenem or cilastatin (Table 4).

To assess for any relationships that may exist between various indices of maturation and either drug's pharmacokinetic profile, all pharmacokinetic parameter estimates were plotted versus these indices and analyzed as a linear or a nonlinear multiple-polynomial function. First-dose imipenem V_{ss} (in liters) and CL and CL_R (both in milliliters per minute) all correlated directly with postconceptual age (r =

TABLE 2. First-dose pharmacokinetics of imipenem in preterm infants

Parameter	Mean ± SD values at imipenem doses (mg/kg) of[a]:			
	10 (n = 5)	15 (n = 14)	20 (n = 11)	25 (n = 9)
$t_{1/2}$ (h)	2.5 ± 0.2	2.6 ± 0.3	2.4 ± 0.3	2.4 ± 0.2
V_{ss} (liters/kg)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.2
AUC (μg · h/ml)	76.1 ± 15.7	114.0 ± 23.6	114.7 ± 31.8	156.8 ± 46.2
CL (ml/min per kg)	2.3 ± 0.3	2.3 ± 0.5	2.4 ± 0.4	2.9 ± 1.0
X_u^{0-12} (% of dose)[b]	26 ± 16	18 ± 7	23 ± 10	18 ± 7
CL_R (ml/min per kg)	0.5 ± 0.3	0.3 ± 0.1	0.5 ± 0.2	0.5 ± 0.2
CL_{NR} (ml/min per kg)	1.8 ± 0.4	1.9 ± 0.5	1.9 ± 0.5	2.4 ± 0.9

[a] n, Number of study infants.
[b] X_u^{0-12}, Amount excreted unchanged in the urine over the 12-h sampling period.

TABLE 3. First-dose pharmacokinetics of cilastatin in preterm infants

Parameter	Mean ± SD values at cilastatin doses (mg/kg) of[a]:			
	10 (n = 5)	15 (n = 14)	20 (n = 11)	25 (n = 9)
$t_{1/2}$ (h)	9.5 ± 3.4	9.5 ± 3.5	9.1 ± 2.7	8.4 ± 2.0
V_{ss} (liter/kg)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
AUC (μg · h/ml)	332.6 ± 93.5	542.2 ± 182.0	745.3 ± 198.6	716.6 ± 180.1
CL (ml/min per kg)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.1	0.6 ± 0.2
X_u^{0-12} (% of dose)[b]	54 ± 34	37 ± 13	46 ± 15	41 ± 12
CL_R (ml/min per kg)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
CL_{NR} (ml/min per kg)	0.4 ± 0.1	0.4 ± 0.2	0.3 ± 0.1	0.4 ± 0.1

[a] n, Number of study infants.
[b] X_u^{0-12}, Amount excreted unchanged in the urine over the 12-h sampling period.

0.57 and $P < 0.001$, $r = 0.72$ and $P < 0.001$, and $r = 0.59$ and $P < 0.001$, respectively). Similar observations were observed for cilastatin (i.e., for V_{ss} [in liters] and CL and CL_R [in milliliters per minute], $r = 0.51$ and $P < 0.001$, $r = 0.61$ and $P < 0.001$, and $r = 0.65$ and $P < 0.001$, respectively). Standardization of these pharmacokinetic parameter estimates by body weight (i.e., V_{ss} [in liters per kilogram] or CL [in milliliters per minute per kilogram]) or body surface area (i.e., V [in liters per meter squared] or CL [in milliliters per minute per meter squared]) essentially abolished any linearity in the observed relationships (i.e., for first-dose imipenem V_{ss} [in liters per kilogram] and CL and CL_R [in milliliters per minute per kilogram], $r = -0.16$, 0.14, and 0.17, respectively, and $P > 0.2$ for all relationships). Similar statistically insignificant relationships were observed when these data were analyzed as a nonlinear polynomial function. Considering the postnatal ages of the infants at the time of the study, the use of gestational age did not alter any of these relationships.

Urinary recovery of imipenem over the 12-h sampling period ranged from 18 to 26% of the dose administered and was independent of the individual dose administered (Table 2). Overall and after these data were pooled, 21 ± 9% (standard deviation) of the dose was excreted unchanged as parent imipenem (Table 5). In contrast, from 37 to 54% of the cilastatin dose was excreted (Table 3), averaging 43 ± 17% (standard deviation) as unchanged drug recovered in the urine. These data and the relative proportion of CL_R and CL_{NR} to CL for these two drugs compared with data described in healthy adult volunteers (5) and adults with severe renal insufficiency (glomerular filtration rate, <4 ml/min) (12) are given in Table 5. Substantial differences were observed in the route by which imipenem was cleared from the bodies of infants compared with that from the bodies of adult volunteers. Imipenem CL_R and CL_{NR}, relative to CL, averaged 16 versus 52% and 80 versus 44%, respectively, in premature infants and adults. Similar but less pronounced differences were observed in the relative proportion to CL for cilastatin CL_R (40 versus 65%) and CL_{NR} (60 versus 34%). Comparison of these data with data obtained in adult patients with severe renal impairment (Table 5) reveals an expected and pronounced dependence on the nonrenal elimination pathway(s) for both imipenem and cilastatin. This dependence on nonrenal elimination is markedly different from data observed in healthy adult volunteers, although it is similar to the elimination characteristics observed in our premature infants.

DISCUSSION

Imipenem represents the first of a new class of carbapenem antibiotics. Similar to other β-lactam antibiotics, imipenem is bactericidal against susceptible bacteria in vitro because it inhibits bacterial cell wall synthesis. Studies of imipenem in vitro have demonstrated a broad spectrum of antibacterial activity, including activity against many β-lactam and aminoglycoside-resistant pathogens as well as the majority of pathogens associated with infections during the neonatal period (1, 4, 8, 14, 15, 19). The *trans* conformation of the hydroxyethyl side chain and hydrogens protects the parent β-lactam structure from inactivation by both penicillinase and cephalosporinase, whereas the alkylthio moiety enhances the compound's in vitro antipseudomonal activity.

Initial disposition evaluations of imipenem in both animals and humans described stable systemic profiles, although they revealed highly variable drug concentrations in urine (1, 4, 8, 13–15, 19). Further studies revealed the rapid and efficient hydrolysis of the imipenem β-lactam ring by the renal brush border enzyme dehydropeptidase I. Cilastatin, a compound that possesses no inherent antibacterial activity and that is a competitive inhibitor of renal dehydropeptidase I (1, 4, 8, 14, 15, 19), is administered concurrently with imipenem to circumvent this renal inactivation. The commercially available preparation contains imipenem and cilastatin in a 1:1 ratio.

The imipenem and cilastatin pharmacokinetic data derived in the present study are similar to the pharmacokinetic parameter estimates described by other investigators, who evaluated older neonates (8, 19). Both groups of investigators described cilastatin concentrations in serum which exceeded those of imipenem as well as markedly prolonged elimination characteristics. As would be expected, the disposition characteristics of imipenem and cilastatin in premature infants are markedly different from those described in children (7, 16). On the average, imipenem and cilastatin

TABLE 4. First-dose and multidose pharmacokinetics of imipenem and cilastatin in preterm infants[a]

Drug (dose[b])	$t_{1/2}$ (h)	V_{ss} (liter/kg)	CL (ml/min per kg)
Imipenem			
FD	2.5 ± 0.3	0.5 ± 0.1	2.5 ± 0.6
MD	2.4 ± 0.3	0.5 ± 0.1	2.3 ± 0.4
Cilastatin			
FD	9.1 ± 2.9	0.4 ± 0.1	0.5 ± 0.2
MD	8.4 ± 4.2	0.5 ± 0.2	0.7 ± 0.2

[a] Values are estimated means ± standard deviations. None of the values were significant in a comparison of first-dose and multidose pharmacokinetic parameters of imipenem and cilastatin.
[b] Abbreviations: FD, first dose (n = 39 infants); MD, multidose (n = 18 infants).

TABLE 5. Comparison of imipenem and cilastatin elimination between premature infants and adults[a]

Parameter	Imipenem			Cilastatin		
	Premature infant	Healthy adult[b]	Renally compromised adult[c]	Premature infant	Healthy adult[b]	Renally compromised adult[c]
$t_{1/2}$ (h)	2.5	0.9	3.7	9.1	0.8	17
X_u^{0-12} (% of dose)[d]	21	54	2.7	43	70	10.5
CL (ml/min per kg)	2.5	5	0.8	4.8	0.16	0.16
CL_R (ml/min per kg)	0.4 (16)[e]	2.6 (52)	0.03 (3.8)	0.2 (40)	3.1 (65)	0.01 (6.3)
CL_{NR} (ml/min per kg)	2 (80)	2.2 (44)	0.77 (97)	0.3 (60)	1.6 (34)	0.14 (87.5)

[a] Values are expressed as means.
[b] Data adapted from reference 5.
[c] Data adapted from reference 12. For renally compromised adults, the glomerular filtration rate was <4 ml/min.
[d] X_u^{0-12}, Amount of drug excreted in the urine over the study interval.
[e] Values in parentheses are a percentage of CL.

elimination from the body is prolonged, and distribution volumes are larger in premature and full-term infants compared with those in children (7, 16).

Statistically significant linear relationships were observed between the primary pharmacokinetic parameter estimates of V_{ss} (in liters) and CL (in milliliters per minute) when correlated with postconceptual age, gestational age, or infant body weight (data not shown). These relationships are similar to those we have reported previously (21) with another antibiotic, vancomycin, for which the CL is primarily dependent on renal function. Considering the dependence of postnatal maturation of glomerular filtration on postconceptual age (versus postnatal age) and the known relationships between body weight and postconceptual age and body water content, these relationships were not unexpected (2, 9, 21). Conversely, when these pharmacokinetic parameter estimates were represented as a function of body weight (i.e., V_{ss} [in liters per kilogram or liters per meter squared] and CL [in milliliters per minute per kilogram or milliliters per minute per meter squared]), these relationships were no longer apparent. This latter finding supports the normalization of drug dosing in premature infants to body weight or body surface area criteria.

Substantial differences were observed in the elimination characteristics of both imipenem and cilastatin when they were compared with values obtained in healthy volunteers (3–6, 11, 12, 20, 23) (Table 5). These differences, most notably, the proportion of CL attributed to CL_R and CL_{NR}, were different for the two compounds; both were different from those observed in healthy adults. The imipenem CL_R and CL_{NR} relative to CL for premature infants averaged 16 and 80%, respectively, compared with adult values, which averaged 52 and 44%, respectively. Likewise, for cilastatin, CL_R and CL_{NR} relative to CL averaged 40 versus 65% and 60 versus 34% in premature infants versus adults, respectively. Conversely, comparison of these elimination characteristics with data described for adults with severely compromised renal function (12) revealed elimination characteristics similar to those observed in our study infants (Table 5). It is possible that these marked differences observed for imipenem CL represented an artifact and were due to improper collection and storage of our samples rather than any true difference in the drug's metabolic disposition. In the performance of our study, however, we made every attempt to minimize the likelihood of such events by rapidly handling all samples and using equal volumes of a plasma and urine stabilizer (see Materials and Methods). Conversely, these findings may reflect biotransformation in serum independent of degradation by renal dehydropeptidase I. Swanson and colleagues (22) described a temperature-dependent degradation of imipenem in vitro in both 0.9% sodium chloride and human serum which was characterized by a first-order process. The results of their study strongly suggest that a portion of the CL_{NR} of imipenem is due to the drug's degradation in serum in vivo. Considering the prolonged elimination characteristics of imipenem observed in our study infants, it appears that this extrarenal biotransformation of imipenem could markedly influence the drug's CL_{NR} and, thus, CL. Furthermore, this reaction may explain, at least partially, the differences observed in the proportions of imipenem CL_R and CL_{NR} to the drug's CL in premature infants compared with those in adults (Table 5).

The data generated in the present study provide a foundation for the design of dosage regimens for imipenem-cilastatin administration for the treatment of bacterial infections arising outside the central nervous system in premature infants. Similar to our previous observations with vancomycin (21), the disposition characteristics of both imipenem and cilastatin are highly variable in premature infants. Using the mean pharmacokinetic parameter estimates for imipenem derived to stimulate immediate postinfusion peak concentrations in serum (using a 30-min infusion duration) averaging 43 mg/liter and 12-h trough concentrations averaging 1.7 mg/liter, we recommend a dose of 20 mg/kg administered every 12 h in infants of ≤36 weeks of postconceptional age. The corresponding cilastatin concentration estimates averaged 83 and 31 mg/liter, respectively. Some investigators (8) have suggested that an imipenem-to-cilastatin ratio of 1:0.25 rather than the currently available 1:1 might achieve equivalent urinary recovery of the antibiotic while minimizing cilastatin accumulation in serum. The potential importance of the observed cilastatin concentrations in serum and the physiologic effects of cilastatin, if any, remain to be elucidated.

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